Editorials

A Picture Is Worth a Thousand Words

PICTURE THIS: Charles Dickens is meeting with his editor in a book-lined room. The editor is looking down his nose disapprovingly, saying, "Come, come, Mr Dickens. Either it is the best of times *or* the worst of times." But Dickens was right. It is both.

To be fair, we have more than ever before: more information available; more ways to help. To be honest, medicine is taking a beating. Taking care of patients is harder. Research and education seem to be faltering. This is a time when we need to pull together, working toward resolving conflicts, affirming principles, and strengthening the links between science, education, and the public. Physicians are the binding force.

Medical journals support the profession as part of that binding force. Their purpose is to inform, to inspire, to raise issues and ask questions, to serve as anchors and boosters. They are the product of devoted effort by many: authors, reviewers, staff members, editors. Because of falling advertising revenue and increasing competition from electronic and popular media and despite economies of desktop publishing and other ways of increasing productivity, the future of medical journals is being questioned. As THE WESTERN JOURNAL OF MEDICINE nears its centennial, we are acutely concerned about its immediate future. Will short-term problems cancel long-term triumphs?

Where does the *Journal* stand? What are we trying to do? What do people say about it? The *Journal*, along with *Annals of Internal Medicine*, *JAMA*, and *The New England Journal of Medicine*, is one of four members in the United States of the Vancouver Group (the International Committee of Medical Journal Editors). The *Journal* has over 43,000 readers across the country and around the world, making it one of the largest peer-reviewed journals. It bridges the entire spectrum of medical practice. It serves a unique function as a forum for medical perspectives in the western United States. It tries to be in the forefront of presenting creative, scientific thought while addressing issues affecting the practice of medicine. Our friends tell us that the *Journal* is a widely respected, reliable, and readable source of practical information for clinicians, both generalists and specialists. Not willing to rest on our laurels, we have plans for the Internet and for book publishing. But, despite accomplishments (and never claiming perfection), the *Journal*'s future is under particular threat. Budgetary and other constraints are calling into question the *Journal*'s continued existence.

Picture this: Priorities swerve away from science and education, away from advocacy for patients and knowledge. Doctor-patient relationships wither; trust wanes. The profession would look like the specters from Dickens's *A Christmas Carol.*

How can we avoid this nightmare? Physicians need to develop a full, robust, vibrant renewal. We need to act on shared values. Right now, we all need to support one another and whatever we have, including THE WESTERN JOURNAL OF MEDICINE, that binds us together, in words and pictures, as a profession. We welcome your comments.

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Chemical Messengers of the Gut

EARLY INVESTIGATIONS of Pavlov detailed how motility and secretion of the gastrointestinal tract were regulated by the nervous system. Elegant descriptions of the cephalic phase of gastric secretion highlighted the importance of neural innervation to the stomach and intestine. During these studies, however, it was also observed that despite cephalic stimulation, little was secreted from the pancreas until acid chyme actually reached the duodenum. This observation was the spark that prompted Bayliss and Starling in 1902 to investigate how the peripheral nervous system might control this intestinal function. Instead, what they discovered was the first hormone. C. J. Martin, Director of the Lister Institute (Middlesex, England), described it thus[1(p902)]:

> I happened to be present at their discovery. In an anesthetized dog, a loop of jejunum was tied at both ends and the nerves supplying it dissected out and divided so that it was connected with the rest of the body only by its blood vessels. On the introduction of some weak HCl into the duodenum, secretion from the pancreas occurred and continued for some minutes. After this had subsided, a few cubic centimeters of acid were introduced into the (de)nervated loop of jejunum. To our surprise, a similarly marked secretion was produced. I remember Starling saying that "it must be a chemical reflex." Rapidly, cutting off a further piece of jejunum, he rubbed its mucous membrane with sand and weak HCl, filtered [it], and injected it into the jugular vein of the animal. After a few moments, the pancreas responded by a much greater secretion than had occurred before. It was a great afternoon.

The substance discovered was named secretin for its ability to stimulate pancreatic juice secretion. The excitement of the discovery is conveyed in this message, although it is unlikely that the investigators realized that their experiments would give birth to an entirely new discipline in physiology, namely endocrinology. Ernest Starling proposed the name "hormones," or chemical messengers, for all such active principals formed in one part of the body and distributed by the circulation to excite the normal functioning or stimulate growth of other parts. This concept revolutionized biologists' understanding of how interrelated gastrointestinal processes could be coordinated by chemical messengers. From that time, research emphasis on neural control of the gut moved to the investigation of hormone transmitters.

As improved methods have been developed for extracting, purifying, and sequencing gastrointestinal hormones, the discovery of peptides exceeded the capability of physiologists to establish their biologic functions in the whole organism. One difficulty in studying gastrointestinal hormones has been the lack of organs, or tissues, with a uniform or high concentration of endocrine cells.

Typically, hormone-secreting cells of the intestine are isolated cells scattered throughout the mucosa. As depicted by Yee and Mulvihill elsewhere in this issue of the journal,[2] hormone-producing cells not only may secrete their transmitters into the bloodstream, but they may act locally through paracrine or autocrine pathways. Although the cellular distribution has provided substantial obstacles for investigators, teleologically this design enables peptide-secreting cells of the gastrointestinal tract to exert both nearby effects, by achieving high concentrations of peptide in the surrounding extracellular environment to regulate nearby cells, and more global effects on distant target tissues as they are transported by the circulation.

To circumvent problems in studying the cellular regulation of gastrointestinal hormone secretion, methods have been developed to enrich cells using elutriation or fluorescence-activated cell sorting. Also, intestinal cell lines and transgenic mouse models are used to explore the regulators of hormone secretion and the pathophysiologic consequences of excess hormone production or hormone deficiency. When combined with organ and tissue preparations and the ability to study brain-gut interactions in whole animals, the relationship between chemical transmitters as hormones and their roles as neurotransmitters can now be better appreciated. It is striking that many peptides originally discovered in the intestine, such as cholecystokinin and substance P, have important physiologic roles in the brain and nervous system. Therefore, some transmitters are produced by endocrine cells of the intestine while the identical peptides can exist in neurons innervating the gut or other organs where they serve as neurotransmitters. Some would interpret the ingenuity of using the same peptide for distinct actions in the gut or brain as evolutionary conservation.

Yee and Mulvihill have provided illuminating examples of the interrelation of peptide transmitters and neural regulation of the gastrointestinal tract. The complementary roles of vasoactive intestinal peptide (VIP) and nitric oxide in esophageal motility and lower esophageal sphincter relaxation enable us to appreciate the pathophysiologic state that produces achalasia when these neurons are lacking. Analogies are drawn to Hirschsprung's disease, where colonic obstruction results from an aganglionic segment involving the internal anal sphincter. This defect in the enteric nervous system results in a deficiency in VIP- and nitric oxide-containing neurons innervating the gut. The authors provide intriguing evidence that peptide transmitters also may be involved in the pathogenesis of other diseases not normally thought of as neuroendocrinopathies of the gastrointestinal tract, such as hypertrophic pyloric stenosis, scleroderma, and inflammatory bowel disease. It is speculated that even irritable bowel syndrome has a hormonal component.

The physiology of several enteric hormones has been elucidated by nature's accidents, whereby a tumor may secrete excess hormone in an unregulated manner. In patients with gastrinoma, gastrin not only causes perilous gastric acid hypersecretion, but also has profound trophic effects on the gastric mucosa.

Although somatostatin inhibits the secretion of most hormones, patients with somatostatin-secreting tumors suffer from diabetes mellitus, providing insight into the relative contribution of somatostatin in the regulation of insulin and glucagon secretion. Other manifestations of somatostatin-secreting tumors such as steatorrhea and gallstones indicate that enteric hormones are critical regulators of normal gastrointestinal function.

Finally, the genetic causes of familial endocrine diseases are within sight of medical geneticists. With the recent identification of the gene responsible for multiple endocrine neoplasia (MEN) type 2,[3,4] the genetic basis for MEN-1 and its associated features of hormone-secreting tumors of the pancreas should provide additional insight into the regulation of gastrointestinal endocrine cell secretion, growth, and neoplasia.

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